Therapeutic Neutrophil Apheresis in Patients With Ocular Behçet Disease

Behçet disease (BD) is an inflammatory disorder of unknown cause with recurrent ocular, vascular, central nervous system, articular, mucocutaneous, and gastrointestinal manifestations. Most manifestations of BD are self-limiting, but repeated attacks of uveitis are a major cause of blindness. Behçet disease is prevalent and is a major cause of morbidity in most Asian nations, countries along the ancient Silk Road, and the Mediterranean basin.

Biopsy specimens from active lesions of BD show large numbers of neutrophils in the absence of infection, and neutrophils from patients with BD show increased superoxide anion production, enhanced chemotaxis, and excessive release of granular enzymes, indicating neutrophil hyperactivity in BD. Similarly, levels of circulating tissue necrosis factor α, interleukin (IL) 1β, and IL-8 are high, and it is believed that these cytokines are involved in neutrophil activation and the enhanced cellular interactions between neutrophils and endothelial cells as a consequences of upregulated expression of adhesion molecules (Mac-1 and intracellular adhesion molecule 1 [ICAM-1]). Therefore, we thought that patients with ocular lesions should respond to therapeutic reduction of neutrophils from peripheral blood by selective adsorption apheresis. This treatment in patients with refractory inflammatory bowel disease has produced dramatic and sustained clinical efficacy together with striking reductions in the amounts of tumor necrosis factor α, IL-1β, IL-6, and IL-8 produced by peripheral-blood leukocytes, the very cytokines that are thought to be involved in the perpetuation of BD.

Methods. Four male patients were given 5 sessions of adsorptive neutrophil apheresis, 1 session per week for 5 consecutive weeks, by means of an adsorptive-neutrophil extracorporeal leukocyte apheresis device (Adacolumn; Japan Immunoresearch Laboratories Co Ltd, Gunma, Japan) filled with cellulose acetate beads, which adsorb neutrophils, monocytes, and a small population of lymphocytes (Fcγ receptors and complement receptors bearing leukocytes). Typically, the column carries adsorb about 65% of neutrophils, 55% of monocytes, and a small fraction of lymphocytes from the blood in the column. Blood from one antecubital vein perfused the column and returned to the patient via the antecubital vein on the contralateral arm. Duration of 1 session was 60 minutes, at 30 mL/min.

The treatment was given according to a study design in which each patient was closely monitored for 6 months before the present treatment and 6 months after the start of this treatment. During each 6-month period, the numbers of major and minor attacks were recorded (Figure). A major attack was defined as an anterior inflammation associated with hypopyon or posterior inflammation associated with retinal exudates extending to more than 2 quarters of the entire retina. A minor attack was defined as a posterior ocular episode of inflammation in 2 quarters of the retina or less, or anterior inflammation without hypopyon. Patients were selected according to the following 4 criteria: (1) a confirmed diagnosis of BD; (2) presence of ocular BD; (3) frequent ocular attacks; and (4) lack of response to high-dose immunosuppressants, or withdrawal of the medication because of severe side effects. Our study design and the treatment outcomes for all 4 cases are presented in the Figure. All patients were receiving colchicine, 0.5 to 1 mg/d, and prednisolone acetate, 5 to 10 mg/d (Table). These medications were continued during the 6 months before and after adsorptive neutrophil apheresis therapy. The study protocol was approved by our institutional ethics committee, and all patients provided informed consent before the initiation of this therapy.

Results. Patients had mild leukocytosis; the mean±SD leukocyte count

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### Patient Characteristics and Treatment Outcome

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Duration of BD, y</th>
<th>Concomitant Medication*</th>
<th>Before New Therapy</th>
<th>6 mo After New Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/32</td>
<td>13</td>
<td>Colchicine, prednisolone</td>
<td>OD 3/100</td>
<td>OD 9/100</td>
</tr>
<tr>
<td>2/M/25</td>
<td>5</td>
<td>Colchicine, prednisolone</td>
<td>Null</td>
<td>Null 1/100</td>
</tr>
<tr>
<td>3/M/20</td>
<td>3</td>
<td>Colchicine, prednisolone</td>
<td>20/60 20/30</td>
<td>20/60 20/25</td>
</tr>
<tr>
<td>4/M/46</td>
<td>14</td>
<td>Colchicine, prednisolone</td>
<td>20/100 CF</td>
<td>20/50 CF</td>
</tr>
</tbody>
</table>

Abbreviations: BD, Behçet disease; CF, counting fingers; HM, hand motions.

*The dosage of prednisolone acetate was 5 to 10 mg/d per patient, while the dosage of colchicine was 0.5 to 1.0 mg/d per patient.
just before this therapy was 10 800 ± 3400 cells/µL, and 89% ± 2% was neutrophils. At 6 months after therapy, the leukocyte count was reduced to 7900 ± 2800 cells/µL, with 67% ± 8% neutrophils. The total number of ocular BD attacks during the 6 months after neutrophil adsorption therapy was decreased in all 4 patients (Figure). The mean ± SD number of attacks was 2.5 ± 0.6 compared with 5.0 ± 1.8 (P = .04) during the preceding 6 months, and 3 of 4 patients were free of major attacks. We evaluated the efficacy of this new treatment by measuring the frequency of ocular attacks rather than changes in visual acuity. This is because many patients with BD have irreversible retinal damage and, therefore, not much can be done to dramatically improve their visual acuity. For these cases, the reduction in frequency of ocular attacks and the prevention of major attacks improved the quality of vision. Nonetheless, the treatment improved visual acuity in all 4 patients (Table). Although this study was not designed to monitor the effect of this therapy on the nonocular manifestations of BD, patients with diarrhea reported cessation of this symptom, and 2 patients with aphthous ulcers had improvement of the ulcers during the treatment. No adverse effects were observed either during the therapy or in the follow-up period.

Comment. Ocular BD is a debilitating condition that affects people throughout the world and responds poorly to drug therapy. Drugs that are frequently given to patients with ocular BD include colchicine, corticosteroids, azathioprine, chlorambucil, cyclophosphamide, and cyclosporine. All of these agents can cause adverse effects, causing the patients to suffer disease symptoms as well as drug toxic effects. In contrast, this new treatment produced no adverse effects in this small study and appeared to be an effective adjunct to conventional therapy for BD. Furthermore, although not specifically investigated, most patients reported feeling better after each neutrophil adsorption session. This is similar to the experience reported during treatment of patients with ulcerative colitis.3

Neutrophil hyperactivity and elevated inflammatory cytokine levels are hallmarks of ocular BD. Neutrophils and monocytes produce inflammatory cytokines, which promote neutrophil activity. This creates a vicious cycle in which elevated and activated neutrophils produce more cytokines and the latter enhance neutrophil activity. When activated neutrophils are eliminated, the prevailing cytokine field may be extinguished. The net effect should be remission of disease. Accordingly, reduction of neutrophils seemed to reduce ocular attacks in our 4 cases. However, evaluation of the full efficacy of this therapy for BD requires more adsorption sessions and determination of the most appropriate frequency of therapy. Furthermore, this procedure does not extensively deplete T cells, which are thought to have a significant role in the posterior ocular attacks.6

In the present study, we did not monitor cytokine profiles, but a study in patients with ulcerative colitis reported a marked reduction in the ability of blood leukocytes to produce inflammatory cytokines.3 More recently published data2 show that neutrophils and monocytes, when adsorbed to the column's cellulose acetate carriers, release large amounts of IL-1 receptor antagonist, which has strong anti-inflammatory effects and is taken to the patients by the returning blood during apheresis therapy.

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3. Hanai H, Watanabe F, Saniabadi F, Matsushita I, Takeuchi K, Iida T. Therapeutic efficacy of...


Myopic Laser-Assisted In Situ Keratomileusis Following Epikeratophakia

A 48-year-old healthy white man underwent bilateral epikeratophakia in 1986 for high myopia. After several months, his refraction regressed slightly and his right cornea developed central haze. He then had photorefractive keratectomy in both eyes for myopia and phototherapeutic keratectomy in the right eye to reduce the corneal haze, which was not successful. Therefore, in March of 1999, the epikeratophakia lenticle was removed from the right cornea to reduce the central corneal haze.

The patient was initially seen in June 2002 for a laser-assisted in situ keratomileusis (LASIK) consult. At that time, the patient’s uncorrected vision was counting fingers OU. Best-corrected vision in the right eye was 20/20-1 with a dry refraction of −7.25−2.50×180 and 20/20 with a cycloplegic refraction of −7.00−1.00×180; in the left eye, it was 20/30+2 with a dry refraction of −8.50−2.00×165 and 20/30+2 with a cycloplegic refraction of −8.00−2.00×165. Pachymetry was 527 μm OD and 672 μm OS. Keratometry was 42.50 diopters (D) at 15 degrees, 44.00 D at 105 degrees OD and 43.75 D at 10 degrees, 45.50 D at 100 degrees OS. Anterior and posterior segment examination results were normal except for corneal neovascularization superiorly and inferiorly in both eyes and midperipheral anterior stromal scarring from the 2-o’clock to the 10-o’clock position in both eyes. Centrally the cornea was clear in both eyes (Figure 1). Corneal topography of the left eye showed a circular midperipheral steepening from the lenticle still present within the cornea (Figure 2).

After much counseling, the patient decided to proceed. On July 11, 2002, LASIK was performed on the left eye. The VISX Star 3 excimer laser (VISX Inc, Santa Clara, Calif) and Hansatome microkeratome (Bausch & Lomb, Rochester, NY) were used. After the flap had been made and lifted in the left eye, a raised ridge of corneal tissue was visible in the midperiphery of the stromal bed. This midperipheral thickening and elevated corneal tissue was presumed to be the previously placed lenticle. The left eye was treated for −7.3−2.00×165. One day postoperatively, uncorrected vision was 20/100 OS. The flap was in good position and clear except for the pre-existing stromal scarring. One week...